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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Brian Seed et al.	Art Unit:	1644
Serial No.:	09/243,008	Examiner:	Patrick J. Nolan
Filed:	February 2, 1999	Customer No.:	21559
Title:	REDIRECTION OF CELLULAR IMMUNITY BY RECEPTOR CHIMERAS		

Commissioner for Patents
Washington, D.C. 20231

APPELLANTS' BRIEF ON APPEAL
SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

In support of Appellants' Notice of Appeal that was filed in connection with the above-captioned case on November 4, 2002, and with reference to the final Examiner's Action that was mailed in this case on July 3, 2002, submitted herewith, in triplicate, is Appellants' Brief on Appeal.

TABLE OF CONTENTS

TABLE OF CASES

Real Party in Interest

The real party in interest in this case is The General Hospital Corporation, to whom all interest in the present application has been assigned by virtue of an Assignment submitted in prior application U.S.S.N. 08/394,176 (recorded on September 13, 1995 at Reel 7768, Frame 0811).

Related Appeals and Interferences

U.S.S.N. 08/488,184, filed on June 7, 1995, which is related to the parent of the present application, is being appealed on different grounds.

Status of Claims

Claims 44-47, 51-52, 56-57, 60-64, 66, 68, 70, 72-75, 77, 79-82, and 92-101 are currently pending. Claims 1-43, 48-50, 53-55, 58, 59, 65, 67, 69, 71, 76, 78, and 83-91 have been canceled. Claims 56-57, 60-64, 66, 68, 70, 77, 80-82, and 92-99 stand withdrawn from consideration. Claims 44-47, 51, 52, 72-75, 79, 100, and 101 were finally rejected in a Final Office Action mailed on July 3, 2002 and are appealed.

Status of Amendments

All amendments have been entered. The present appeal is based on the pending claims as reproduced in Appendix A.

Summary of the Invention

Appellants' invention features cells expressing a combination of immune cell chimeric receptors and CD28 chimeric receptors. The immune cell chimeric receptors signal target cell destruction through a transmembrane domain, rather than a cytoplasmic (intracellular) domain, as is described, for example, at page 48, line 20, to page 50, line 10 of the specification and in Figures 8A, 8B, 9A, and 9B. Such receptors, working together with CD28 chimeric receptors (as described, e.g., at page 59, line 6, to page 60, line 11), direct the recognition and destruction of specific targets, such as pathogens or cells infected with pathogenic agents such as HIV.

Issue

The sole issue on appeal is whether the Examiner erred in rejecting claims 44-47, 51, 52, 72-75, 79, 100, and 101 based on the written description requirement of 35 U.S.C. § 112, first paragraph.

Grouping of Claims

The claims stand or fall together.

Argument

As is clear from the Issue section above, the pending claims stand rejected on the grounds of a lack of written description. This rejection, as applied in the final Office Action, and Appellants' response to these rejections is now presented.

The Written Description Rejection Should be Reversed

Appellants' invention features cells expressing a combination of immune cell chimeric receptors and CD28 chimeric receptors. Such receptors direct the recognition and destruction of specific targets, e.g., pathogens or cells infected with pathogenic agents such as HIV. This invention is claimed in claims 44 and 79, as well as their dependent claims.

Claim 44, as filed, was directed to a cell which expresses at least two proteinaceous membrane-bound chimeric receptors where the first receptor includes an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signaling the cell to destroy a receptor-bound target cell or a receptor-bound target infective agent, and the second receptor includes an extracellular portion which is capable of specifically recognizing and binding the target cell or target infective agent and an intracellular portion which is derived from CD28.

Claim 79, as filed, was directed to a cell which expresses at least two proteinaceous membrane-bound receptors, where the first of these receptors includes an extracellular portion which is capable of recognizing and binding a target cell or target infective agent, and a transmembrane portion derived from a T cell receptor CD3, zeta, or eta polypeptide, a B cell receptor, or an Fc receptor, and where the second receptor includes an extracellular portion which is capable of specifically recognizing and binding the target cell or target infective agent and an intracellular portion which is derived from CD28.

In response to the first Office Action, Appellants amended claim 44 to emphasize that the transmembrane domain is responsible for signaling by adding the phrase "in the absence of an intracellular signalling domain" to part (b). To further highlight this point, Appellants also added part (c) to claims 44 and 79 which recites that the receptor includes "an intracellular domain that does not signal said cell to destroy said receptor-bound target cell or receptor-bound target infective agent." As was noted in Appellants' reply, these amendments are fully supported by the original specification, for example, at page 48 and by Figures 8A and 8B.

I. Legal Standard

To satisfy the written description requirement, one need only communicate to those skilled in the art that the claimed subject matter is intended to be part of their

invention. As stated by the Federal Circuit in *Martin v. Mayer*, 823 F.2d 500, 3 U.S.P.Q.2d 1333 (Fed. Cir. 1987):

> [T]he specification must 'convey clearly to those skilled in the art to whom it is addressed ... the information that [the inventor] has invented the specific subject matter later claimed.'

Moreover, the M.P.E.P. (§ 2163.02; Eighth Edition, August 2001) states:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she has invented what is claimed."

To satisfy this standard, the Federal Circuit has held that the specification need only convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). As set forth below, Appellants' specification meets this standard for the presently claimed invention.

II. Original Claim 44 Is Directed to a Chimeric Receptor Having a Transmembrane Signaling Domain

Claims 44-47, 51, 52, 72-75, 79, 100, and 101 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that is not described in the specification. In the final Office Action, the Office states (page 3):

> [O]riginally filed claim 44 has only 2 parts to the receptor: A) an extracellular domain and B) a transmembrane domain. There is no recitation of the intracellular domain in the

originally filed claims.

Appellants note that original claim 44 recites "a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signalling said cell to destroy a receptor-bound target cell or a receptor-bound target infective agent" (emphasis added). The amendments made to claims 44 and 79 during the prosecution of the application do no more than highlight the fact that it is the transmembrane domain that signals, and that the intracellular domain does not signal the cell to destroy a receptor-bound target cell or receptor-bound target infective agent. In particular, Appellants amended claim 44 to highlight that the transmembrane domain is capable of signaling by adding the phrase "in the absence of an intracellular signalling domain" to part (b), and by adding part (c) to claims 44 and 79 which recites that the receptor includes "an intracellular domain that does not signal said cell to destroy said receptor-bound target cell or receptor-bound target infective agent." The fact that the transmembrane domain is capable of signaling target destruction is supported by originally filed claim 44, and, on this basis alone, the rejection should be reversed.

III. Appellants' Specification Includes a Working Example of a Chimeric Receptor Having a Transmembrane Signaling Domain

In the final Office Action, the Office further asserts (page 2, page 3):

> The remaining issue if whether Applicant's disclosure of one species, among a myriad amount of receptor cell constructs conveys to one of skill in the art at the time of the invention

Applicant's presently claimed sub-genus.

* * *

> The disclosure of one working example, a tripeptide intracellular domain, that inherently does not signal said cell to destroy a receptor bound target-cell or receptor-bound target infective agent, does not support a sub-genus claim that in its scope is between original claim 44, where any intracellular domain could be added or not be added and applicants lone working example ... It is clear from the multitude of receptor constructs disclosed in the originally filed specification that Applicant's recitation of a cell that has three parts to a receptor, one extracellular domain, one transmembrane domain, and any intracellular domain that does not signal said cell to destroy a receptor bound target-cell or receptor-bound target infective agent, was not part of Applicant's originally filed disclosure.

Appellants respectfully disagree. The Office concedes that Appellants' original specification provides a working example of the presently claimed invention. With regard to the creation of a sub-genus, Appellants disagree with the assertion that the present claims are directed to a subgenus that is not described in the specification. As noted above, Appellants' specification has from its original filing date described and claimed chimeric receptors that signal through their transmembrane domains. For example, at page 48, lines 20-33, a number of chimeras having intracellular domains of reduced length are described. One such chimera, disclosed at lines 31-33 and in Figure 8A, possesses a transmembrane domain joined to an intracellular domain of only three amino acid residues (amino acids 31-33; RVK). This chimeric receptor is capable of signaling and does so through its transmembrane domain, its intracellular domain merely

anchoring the chimera in the cell membrane.

Moreover, in the Declaration by Dr. Brian Seed, submitted with Appellants' reply to the Office Action mailed on October 23, 2001, Dr. Seed attests to the fact that these three intracellular amino acids do not signal, but rather anchor the chimera in the cell membrane. Dr. Seed also states that his data indicate that signaling by this chimeric receptor is mediated by the transmembrane domain, precisely as claimed in original and instant claims 44 and 79 and their dependent claims. As Appellants' specification provides a working example of a chimeric receptor that signals through a transmembrane (and not an intracellular) domain, precisely as specified by the present amended claims, the specification and claims, prior to the present amendments, clearly included these features; no sub-genus has been created.

IV. The Written Description Rejection Has Been Satisfied in the Present Application

Appellants submit that, to fulfill the written description requirement, one need only communicate to those skilled in the art that the claimed subject matter is intended to be part of their invention. As stated by the Federal Circuit in *Martin v. Mayer*, 823 F.2d 500, 3 U.S.P.Q.2d 1333 (Fed. Cir. 1987):

> [T]he specification must 'convey clearly to those skilled in the art to whom it is addressed ... the information that [the inventor] has invented the specific subject matter later claimed.'

To satisfy this standard, the Federal Circuit has held that the specification need only convey with reasonable clarity to a skilled artisan that the inventor "was in possession of the invention" at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991).

Appellants' specification plainly meets the written description standard by providing a working example of a chimeric receptor that signals through a transmembrane, rather than an intracellular, domain. Moreover, Appellants have, from the time they originally filed this application, claimed this type of receptor as part of their invention. One skilled in the art therefore certainly would recognize that, at the time of filing, the inventors were in possession of chimeric receptors that signaled through transmembrane (rather than intracellular) domains. The written description requirement of § 112, first paragraph has been satisfied by Appellants, and the rejection of claims 44-47, 51, 52, 72-75, 79, 100, and 101 under § 112, first paragraph, should be reversed.

Conclusion

Appellants respectfully request that the rejection of claims 44-47, 51, 52, 72-75, 79, 100, and 101 be reversed. Enclosed is a check for $320.00 in payment of the fee required by 37 C.F.R. § 1.17(c). Also enclosed are a petition to extend the period for submitting an Appeal Brief for three months, to and including April 4, 2003, and a check for $930.00 in payment of the extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 3, 2003

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Appendix A: Claims on Appeal

44. (Twice Amended) A cell which expresses at least two proteinaceous membrane-bound chimeric receptors,

the first of said receptors comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, (b) a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor protein which, in the absence of an intracellular signalling domain, is capable of signalling said cell to destroy a receptor-bound target cell or a receptor-bound target infective agent, and (c) an intracellular domain that does not signal said cell to destroy a receptor-bound target cell or receptor-bound target infective agent; and

the second of said receptors comprising (a) an extracellular portion which is capable of specifically recognizing and binding said target cell or said target infective agent, and (b) an intracellular portion which is derived from CD28.

45. The cell of claim 44, wherein, following binding of said extracellular portion to said cell or agent, said transmembrane portion oligomerizes with a cytolytic signal-transducing protein of said receptor-bearing cell resulting in destruction of said receptor-bound agent or cell.

46. The cell of claim 44, wherein said binding is MHC-independent.

47. The cell of claim 44, wherein said transmembrane portion comprises an oligomerizing portion of a T cell receptor protein, a B cell receptor protein, or an Fc receptor protein, or a functional derivative thereof.

51. (Amended) The cell of claim 101, wherein said T cell receptor protein is ζ.

52. The cell of claim 51, wherein said chimeric receptor comprises amino acids 400-420 of SEQ ID NO:6.

72. (Amended) The cell of claim 44, wherein said extracellular portion comprises the ligand-binding portion of a receptor, the receptor-binding portion of a ligand, the antigen-binding portion of an antibody, or a functional derivative thereof.

73. (Amended) The cell of claim 44, wherein said target infective agent is an immunodeficiency virus or said target cell is a host cell infected with an immunodeficiency virus.

74. The cell of claim 73, wherein said extracellular portion comprises an HIV envelope-binding portion of CD4, or a functional derivative thereof.

75. The cell of claim 73, wherein said HIV-envelope binding portion of CD4 comprises the peptide encoded by nucleotides 1-369 of SEQ ID NO:1.

79. (Amended) A cell which expresses at least two proteinaceous membrane-bound chimeric receptors,

the first of said receptors comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) a transmembrane portion derived from a T cell receptor CD3, zeta, or eta polypeptide, a B cell receptor, or an Fc receptor, and (c) an intracellular domain that does not signal target cell or target infective agent destruction; and

the second of said receptors comprising (a) an extracellular portion which is capable of specifically recognizing and binding said target cell or said target infective

agent, and (b) an intracellular portion which is derived from CD28.

100. The cell of claim 44, 92, or 93, wherein said cell destroys said receptor-bound target cell or target infective agent by cytolysis.

101. The cell of claim 44, wherein said transmembrane portion of the first of said receptors is derived from a T cell receptor protein.